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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/528,644	03/20/2000	Lars Thim	3951.224-US	5698

23650 7590 01/19/2005

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EXAMINER	
ROMEO, DAVID S	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 01/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/528,644	THIM ET AL.	
	Examiner	Art Unit	
	David S Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *66 and 67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *66 and 67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 11/03/2004 has been entered. Claims 66 and 67 are pending and being examined. The double patenting rejection is no longer applicable to the present claims.

New Formal Matters, Objections, and/or Rejections:

Claim Rejections - 35 USC § 103

Claim 66 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tomasetto (2, cited by Applicants) in view of Hitzeman (X, the paper mailed 07/20/2001), Onda (the paper mailed 07/20/2001), Strausberg (the paper mailed 05/03/2004), Gelfand (the paper mailed 05/03/2004), and Grinna (U, the paper mailed 01/2005).

Tomasetto discloses the cDNA and deduced amino acid sequence of a human spasmolytic polypeptide (hSP) (paragraph bridging pages 409-410; Figure 5). The encoded protein contains a putative signal sequence, amino acids 1-24 (Figure 5). The amino acid sequence of the encoded protein minus the putative signal peptide is identical to SEQ ID NO:1 of the present claims, as indicated below (Qy = Applicants' SEQ ID NO: 1) (Db = hSP):

```
RESULT    1
ENTRY             S12371     #type fragment
TITLE             spasmolytic protein 1 precursor - human (fragment)
ALTERNATE_NAMES   trefoil factor 2
ORGANISM          #formal_name Homo sapiens #common_name man
DATE              21-Nov-1993 #sequence_revision 24-May-1996 #text_change
                    18-Sep-1998
ACCESSIONS        S12371
REFERENCE         S12371
   #authors       Tomasetto, C.; Rio, M.C.; Gautier, C.; Wolf, C.; Hareuveni,
                    M.; Chambon, P.; Lathe, R.
   #journal       EMBO J. (1990) 9:407-414
   #title         hSP, the domain-duplicated homolog of pS2 protein, is
                    co-expressed with pS2 in stomach but not in breast
                    carcinoma.
   #cross-references MUID:90151615
   #accession     S12371
```

```
      ##molecule_type mRNA
      ##residues      1-130 ##label TOM
      ##cross-references EMBL:X51698; NID:g36558; PID:g36559
GENETICS
   #gene         GDB:TFF2; SML1
      ##cross-references GDB:128989; OMIM:182590
   #map_position 21q22.3
FUNCTION
   #description  inhibits gastrointestinal motility and gastric acid secretion
CLASSIFICATION   #superfamily spasmolytic protein; trefoil homology
KEYWORDS         duplication; hormone; pancreas
FEATURE
   1-24               #domain signal sequence (fragment) #status predicted
                        #label SIG\
   25-130             #product spasmolytic protein #status predicted #label
                        MAT\
   32-73              #domain trefoil homology #label TRF1\
   82-122             #domain trefoil homology #label TRF2\
   30-128,32-59,43-58,
   53-70,82-108,
   92-107,102-119     #disulfide_bonds #status predicted
SUMMARY          #length 130  #checksum 8997

  Query Match          100.0%;  Score 857;  DB 1;  Length 130;
  Best Local Similarity 100.0%;  Pred. No. 6.82e-177;
  Matches   106;  Conservative    0;  Mismatches   0;  Indels   0;  Gaps   0;

Db     25 EKPSPCQCSRLSPHNRTNCGFPGITSDQCFDNGCCFDSSVTGVPWCFHPLPKQESDQCVM 84
        ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Qy      1 EKPSPCQCSRLSPHNRTNCGFPGITSDQCFDNGCCFDSSVTGVPWCFHPLPKQESDQCVM 60

Db     85 EVSDRRNCGYPGISPEECASRKCCFSNFIFEVPWCFFPNSVEDCHY 130
        |||||||||||||||||||||||||||||||||||||||||||||||
Qy     61 EVSDRRNCGYPGISPEECASRKCCFSNFIFEVPWCFFPNSVEDCHY 106.
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hSP contains the amino acid sequence Asn-X-Ser/Thr, wherein X is any amino acid, at amino acid residues 39-41, which is a classic N-linked glycosylation site, as evidenced by Hitzeman. Specifically, Hitzeman teaches N-linked glycosylation at the amino acid sequence Asn-X-Ser/Thr wherein X is any amino acid (page 436, full paragraph 2). Amino acid residues 39-41 of hSP correspond to amino acids 15-17 of Applicants' SEQ ID NO:1. Tomasetto discloses strong conservation of primary structure between PSP, mSP and hSP which suggest that these three proteins fulfill similar biological functions (page 412, column 2, full paragraph 4). Tomasetto suggests purifying hSP (page 413, left column, last paragraph of discussion). Tomasetto does not teach, in the sense that Tomasetto does not anticipate, an isolated hSP polypeptide which has an amino acid sequence according to SEQ ID NO: 1 and which is N-glycosylated with $(GlcNAc)_2(Man)_{10\text{-}15}$ at the Asn in position 15 of SEQ ID NO: 1.

Onda discloses a polypeptide having high homology with pancreatic spasmolytic polypeptide (PSP) and expects it to fulfill similar biological functions (page 6, full paragraph 3). Onda discloses the expression and secretion of the recombinant human polypeptide in E. coli, yeast cells, and animal cells (page 3, full paragraph 1; page 4, line 55; sentence bridging pages 4-5; page 5, lines 8-9 and 31-34; Example 5, pages 9-10).

The use of yeasts such as Saccharomyces as hosts for expressing mammalian and other foreign proteins offers advantages lacking in more commonly used prokaryotic hosts such as Escherichia coli. See Strausberg, column 1, full paragraph 2.

Mammalian cells are more difficult to culture than yeast. See Gelfand, column 2, lines 29-30.

Grinna teaches that on heterologous invertase produced in P. pastoris, approximately 85% of the oligosaccharides are in the size range $Man_{8-14}GlcNAc_2$. The largest oligosaccharides isolated from P. pastoris are significantly shorter than the hypermannosylated structures typical of S. cerevisiae, indicating that the factors which influence the processing of N-linked oligosaccharides in P. pastoris are different from those which influence processing in S. cerevisiae. The smaller N-linked oligosaccharides synthesized by P. pastoris resemble high-mannose oligosaccharides synthesized by animal cells, and this finding increases the utility of P. pastoris as a host for the production of heterologous glycoproteins. See the Abstract.

Onda, Strausberg, Gelfand, and Grinna do not teach an isolated hSP polypeptide which has an amino acid sequence according to SEQ ID NO: 1 and which is N-glycosylated with $(GlcNAc)_2(Man)_{10-15}$ at the Asn in position 15 of SEQ ID NO: 1.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to purify hSP, as suggested by Tomasetto, and to modify that teaching by expressing hSP recombinantly in P. pastoris, as taught by Grinna, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because the supply of many eukaryotic proteins which have potential clinical or industrial use is often limited by their low natural availability. Gene cloning and expression in (E. coli, bacteria, yeast, etc.) would provide a more abundant source of these polypeptides. One of ordinary skill in the art would be motivated to combine these teachings because the advantages of recombinant expression would provide a convenient source of readily purified protein. One of ordinary skill in the art would be motivated to use yeast for the recombinant expression of hSP because the use of yeasts such as Saccharomyces as hosts for expressing mammalian and other foreign proteins offers advantages lacking in more commonly used prokaryotic hosts such as Escherichia coli and because mammalian cells are more difficult to culture than yeast.. One of ordinary skill in the art would be motivated to use P. pastoris for the expression of hSP because the largest oligosaccharides isolated from P. pastoris are significantly shorter than the hypermannosylated structures typical of S. cerevisiae and because the smaller N-linked oligosaccharides synthesized by P. pastoris resemble high-mannose oligosaccharides synthesized by animal cells, and this finding increases the utility of P. pastoris as a host for the production of heterologous glycoproteins. In so doing one of ordinary skill in the art would reasonably expect to obtain an isolated hSP polypeptide which has an amino acid sequence according to SEQ ID NO: 1 and which is N-glycosylated with $(GlcNAc)_2(Man)_{8-14}$ at the Asn in position 15 of SEQ ID NO: 1. The

claimed $Man_{10-15}GlcNAc_2$ overlaps the $Man_{8-14}GlcNAc_2$ disclosed by the prior art. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. See M.P.E.P. 2144.05(I). The invention is prima facie obvious over the prior art.

Claims 66 and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomasetto (2, cited by Applicants) in view of Hitzeman (X, the paper mailed 07/20/2001), Onda (the paper mailed 07/20/2001), Strausberg (the paper mailed 05/03/2004), Gelfand (the paper mailed 05/03/2004), and Grinna (U, the paper mailed 01/2005) as applied to claim 66 above and further in view of Jorgensen (U, the paper mailed 05/03/2004).

Tomasetto in view of Hitzeman, Onda, Strausberg, Gelfand, and Grinna teach an isolated hSP polypeptide which has an amino acid sequence according to SEQ ID NO: 1 and which is N-glycosylated with $(GlcNAc)_2(Man)_{8-14}$ at the Asn in position 15 of SEQ ID NO: 1. Tomasetto in view of Hitzeman, Onda, Strausberg, Gelfand, and Grinna do not teach a pharmaceutical composition comprising an isolated hSP polypeptide which has an amino acid sequence according to SEQ ID NO: 1 and which is N-glycosylated with $(GlcNAc)_2(Man)_{8-14}$ at the Asn in position 15 of SEQ ID NO: 1 together with a pharmaceutically acceptable carrier or excipient.

Jorgensen teaches a pharmaceutical composition comprising PSP and a pharmaceutically acceptable carrier (page 232, full paragraphs 1 and 2; page 233, full paragraph 2; paragraph bridging pages 233-234; page 234, full paragraph 1). PSP inhibits gastrointestinal motility and gastric acid secretion (page 231, full paragraph 1).

PSP is atoxic and effective after oral administration. PSP may possess a potential utility in the treatment of gastro-duodenal ulcer diseases. Page 243, full paragraph 1. Jorgensen does not teach an isolated hSP polypeptide which has an amino acid sequence according to SEQ ID NO: 1 and which is N-glycosylated with $(GlcNAc)_2(Man)_{8-14}$ at the Asn in position 15 of SEQ ID NO: 1.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make an isolated hSP polypeptide which has an amino acid sequence according to SEQ ID NO: 1 and which is N-glycosylated with $(GlcNAc)_2(Man)_{8-14}$ at the Asn in position 15 of SEQ ID NO: 1, as taught by Tomasetto in view of Hitzeman, Onda, Strausberg, Gelfand, and Grinna, and to modify that teaching by making a pharmaceutical composition, as taught by Jorgensen, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to combine these teachings because PSP, mSP and hSP display a strong conservation of primary structure, which suggest that these three proteins fulfill similar biological functions, because PSP may possess a potential utility in the treatment of gastro-duodenal ulcer diseases, and it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to test the potential utility of hSP in the treatment of gastro-duodenal ulcer diseases. The invention is prima facie obvious over the prior art.

Response to Arguments

Applicants argue that there is nothing in the cited art that teaches that the $(GlcNAc)_2(Man)_{10-15}$ structure might be attached to the Asn 15 of SEQ ID NO: 1 upon recombinant expression in yeast. Applicant's arguments have been fully considered but

they are not persuasive. The claimed $Man_{10-15}GlcNAc_2$ structures overlaps the $Man_{8-14}GlcNAc_2$ structures disclosed by the prior art. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. See M.P.E.P. 2144.05(I). The examiner believes he has addressed all pertinent arguments.

Conclusion

No claims are allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, BRENDA BRUMBACK, CAN BE REACHED ON (571) 272-0961.

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ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
JANUARY 18, 2005